REMARKS

Claims 49-61, 63-66, and 68-72 are pending. Claims 49, 58, 59, 66, 70, and 72 have been amended. Claim 71 has been canceled. No new matter has been added as a result of the amendments.

Priority Claim

The Examiner has determined that "...claims 49-61, 63-66 and 71 are only entitled **at best to the effective filing date of 3/9/1999** because the provisional application 60/077,262 does not have a written support for the administration of a stem cell factor (SCF) into any mammal or a concept for a co-administering any colony stimulating factor (CSF) other than a GM-CSF with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof."

Claim 49 has been amended and claim 71 canceled. Accordingly, Applicants respectfully request that the Office's objection to the priority claim with respect to claims 49-61, 63-66, and 71 be withdrawn.

Claim Objections

Claims 58 and 59 have been amended to address the Examiner's objection to the repetition of the term "EPC" in the language of the claims.

Rejections under 35 U.S.C. § 112

The Office rejects claim 72 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Claim 72 has been amended, so that it no longer depends from previously canceled claim 67, and so that the term "factor" has been substituted with the terms "fragment thereof". Accordingly, Applicants respectfully request that the Office's present objection to claim 72 be withdrawn.

Of note, claim 66 has likewise been amended, so that the term "factor" has been substituted with the terms "fragment thereof".

Rejections under 35 U.S.C. § 103(a)

The Office rejects claims 49-61, 63-66, and 68-72 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 97/14307 (hereinafter referred to as "Isner") in view of U.S. Patent No. 5,880,090 (hereinafter referred to as "Hammond"). Specifically, the Examiner alleges:

> . . . it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering to the treated mammal an effective amount of at least one of SCF or CSF or an effective amount thereof in light of the teachings of Hammond et al, and since Isner also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is also an angiogenic protein or factor . . . (Office action mailed February 22, 2007, page 7, second paragraph).

As per the Examiner, "Isner does not specifically teach the administration of an effective amount of a. . . colony stimulating factor. . . into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein . . .. " (Office action, mailed February 22, 2007, page 6, second paragraph). The Examiner then looks to Hammond to provide the requisite motivation to modify Isner.

Applicants maintain that Hammond does not teach or suggest a method for treating myocardial ischemia. Rather, Hammond is directed to methods for enhancing the endothelialization of synthetic prosthetic vascular grafts. Applicants further respectfully reiterate that Hammond, in fact, teaches away from employing their methods for promoting endothelialization. In the previously filed response, Applicants suggested the Office refer to Example 1, where Hammond describes adverse results associated with the endothelialization of grafts, thus teaching away from the use of such methods. The Examiner alleges, in the presently pending Action, that "Since examples 3 and 4 did not mention anything about the presence of microcalcification, this means that microcalcification was not a problem (Office action mailed February 22, 2007, page 9, first paragraph). Applicants respectfully disagree.

According to Example 3, two dogs that received G-CSF had 80% and 35% of the graft surfaces covered with endothelial-like cells (ELC). Although Example 1 shows similar results with respect to endothelialization, Example 1 immediately draws attention to the undesirable side effects associated with the autologous bone marrow blood (BMB) grafts – osteoblasts,

osteocysts, and microcalcification revealed by histological studies. Example 3 iterates the % coverage of graft surfaces with ELC, but clearly states that "Qualitatively, the nature of these surface cells will be evaluated histologically by light microscopy...as well as by electron microscopy." (column 9, lines 44-47). In other words, Example 3 does not mention microcalcification, because no histological analysis has been done, but the Example's discussion of the future histological studies indicate their importance in evaluation of the graft endothelialization. If the person of ordinary skill in the art were to make any assumption about presence or lack of microcalcification, such an assumption would be based on actual results (i.e., Example 1), results showing that microcalcification was, indeed, present.

The same holds for Example 4, a wholly hypothetical example that likewise calls for histological analysis of the surface cells (column 10, lines 16-19). Thus, the person of ordinary skill in the art *would* recognize the negative side-effects of Hammond's endothelialization of synthetic grafts and be taught away from putting the same methods to use. In view of this teaching away, that same person would lack the requisite motivation to introduce changes based in Hammond to the methods of Isner, let alone possess the expectation of success required to introduce such changes.

In addition to describing negative side-effects associated with their method of promoting endothelialization using BMB grafts, Hammond failed to appreciate how the effect on endothelialization was achieved. Far from teaching that GM-CSF was sufficient to mobilize EPCs, Hammond actually teaches away from such a conclusion. In column 8, lines 16-22, Hammond states that "...the BMB used for seeding also contained many types of cells that are capable of releasing a **variety of growth factors that may have contributed to the observed endothelialization**..." Hammond fails to teach that GM-CSF should be used to enhance endothelialization, much less teaching that GM-CSF should be used to treat an ischemic myocardial tissue. In fact, Hammond teaches that a significant amount of experimentation should be undertaken to determine the factors that contribute to endothelialization. Thus, contrary to the Examiner's allegation that Applicants results are not unexpected or surprising in view of Hammond, Hammond fails to appreciate that GM-CSF is sufficient to treat an ischemic tissue. Rather, Hammond believes that further research is required to determine which growth factors contributed to the observed effect.

For the reasons iterated above, the skilled person would lack the requisite motivation to modify Isner to arrive at the treatment methods of the present application based on the teachings of Hammond.

The Office further rejects claims 49-61, 63-66, 68-70, and 72 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 97/14307 (hereinafter referred to as "Isner") in view of J Clin Invest 87:986-995, 1991 (hereinafter referred to as "Bussolino"). Specifically, the Examiner alleges that "...it would have been obvious for an ordinary skilled artisan to modify the method of Isner by utilizing recombinant G-CSF and/or GM-CSF as an endothelial cell mitogen to be administered to a patient in need thereof in light of the teachings of Bussolino et al..."

Applicants maintain that Bussolino neither teaches nor suggests a method for treating myocardial ischemia. Rather, Bussolino describes a study that seeks to characterize endothelial cell functions modulated by G- and GM-CSF. In fact, "study" is certainly the correct term for describing Bussolino because Bussolino fails to draw virtually any significant conclusion relating to the observed results. For example, Bussolino states "...we wanted to obtain **initial** indications as to the capacity of this cytokine to act in concert with bFGF (page 994, right column, lines 10-12); "...we observed responses whose intensity is **suggestive** of a cooperative interaction of the two cytokines... (page 994, right column, lines 13-15);" and "This **initial observation needs to be extended** (page 994, right column, lines 18-19)." Bussolino clearly indicates that his studies are only preliminary, and much additional work needs to be done before these results may be applied as a method of treatment. Bussolino clearly teaches that additional studies must be undertaken to determine those endothelial cell functions modulated by G- and GM-CSF. The skilled artisan provided with Bussolino would lack the requisite expectation of success to employ the experimental methods to treat myocardial ischemia.

The standard in determining obviousness is not whether certain experiments ***could be tried***, but whether the prior art suggested that the modifications ***should be made***, and further suggested that the modified methods ***would function successfully***. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir.,1988). Instead of providing the motivation or expectation of success required to adapt the methods of Isner to ultimately treat myocardial ischemia, Bussolino merely

provides motivation to undertake further studies. Thus, contrary to the Examiner's assertions, Bussolino fails to predict the surprising results observed by Applicant. Specifically, Bussolino fails to predict that combination therapy using a vascularization modifying agent, such as GM-CSF, and an angiogenic protein would provide a synergistic effect.

In summary, none of the references cited by the Office, alone or in any combination, teaches or suggests that one should administer GM-CSF in combination with an angiogenic factor for the treatment of an ischemic myocardial tissue. It is not sufficient that one ***could*** have made the combination, the cited references must suggest the desirability of making the claimed combination and must further indicate that the combination, if made, would have succeeded.

Indeed, Applicants were the first to appreciate that myocardial ischemia could be treated by injecting a myocardial tissue with a nucleic acid encoding an angiogenic factor and administering GM-CSF or SCF. The Office has failed to establish a *prima facie* case of obviousness, and the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

Double Patenting Rejections

Claims 49, 69, and 71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 50-51 and 57-59 of co-pending U.S. Application No. 10/696,391.

Claims 49-61, 63-66, and 68-72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52, 54-56, 60-65, and 68 of co-pending U.S. Application No. 10/696,391.

Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double patenting rejections will be the only rejections remaining in the instant application. Therefore, pursuant to M.P.E.P. §822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

CONCLUSION

In view of the above Amendment and Remarks, Applicants believe the pending application is in condition for allowance. If the Examiner disagrees, Applicants respectfully request that the Examiner contact the undersigned agent by telephone to schedule an interview prior to the mailing of an Office action.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Dated: July 23, 2007

Respectfully submitted,

By _____

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